REMARKS

IDS

A new IDS will be filed in the near future.

Election/Restriction

Method claims not within the elected group are cancelled without prejudice or disclaimer.

The Examination of withdrawn method claims 7, 8 and 10 is respectfully and courteously requested.

Each of these claims recites additional ingredients and each explicitly requires the particulars of the elected methods, i.e., each of these claims is dependent on the elected method claim 1.

No further or only a minimal search effort would be needed to examine the subject matter of these withdrawn claims as they should at least be patentable for at least the same reasons as the claim they depend upon.

Claim Rejections Under 35 USC § 112

The methods directed to the "prevention" of diseases have been cancelled without prejudice or disclaimer rendering the rejection thereof moot.

The Office Action rejects the method of treatment claims as allegedly not enabled with the exception of atopic dermatitis and the treatment of viral warts.

Atopic dermatitis is the subject of example 1 and viral warts are the subject of example 2. Applicants also point to example 3, which is directed to acne vulgaris. The Office Action appears to have missed this example. Separate claims are directed to the treatment of each of these exemplified indications.

The Office Action alleges that "the skilled artisan would view that the treatment of all inflammatory skin or mucous membrane diseases using one composition is highly unlikely." As support, the Office Action provides various examples of inflammation and various causes/mechanisms thereof. The Office Action also cites Leshchinskii et al. from 1972, teaching that some drugs exhibit anti-inflammatory effect in some models but not on others possibly because of the differences in the action of the factors producing the inflammation.

The date of the reference relied upon precedes the filing date of the present application (which is the relevant time for analyzing enablement in view of the state of the art

at such time) by more than three decades. Certainly, the state of the art has changed significantly since 1972.

Nevertheless, applicants address the allegations on the merits also. Leshchinskii et al. never teaches or even remotely suggests that there are no broad scope anti-inflammatory drugs in the art, but rather teaches that some drugs that affect different factors of inflammation don't perform consistently in different models. In this regard, Leshchinskii et al. explicitly teaches that the mechanism of action of drugs was investigated by the use of different models. Thus, the study was highly related to mechanism of action investigation as can be clearly seen in the disclosure of the entire reference.

Moreover, as one could see, as far back as 1972 the state of the art relating to inflammation was quite advanced. Leshchinskii et al. describes using six models of inflammation and investigating the mechanisms thereof.

Also, just because various types of inflammation and various types of causes are possible, does not lead one of ordinary skill in the art to the conclusion that there are no drugs with broad indications generally being able to target various types of inflammation.

To the contrary, the application provides three examples of successful treatment of very different types of inflammation, i.e., examples 1, 2 and 3 show hyaluronic acid in crosslinked form to be suitable for treating different inflammatory skin diseases independently from their origin. Atopic dermatitis (example 1) is a disease primarily aggravated by contact with or intake of allergens and is believed to also involve genetic predisposition. On the other hand, viral warts (example 2) are caused by a viral infection. And acne vulgaris (example 3) is a result of changes in the pilosebaseous units of the skin.

The application of hyaluronic acid in crosslinked form for the treatment of very different inflammatory skin diseases, on the other hand, is believed to be the result of the drug's mode of action which is believed to involve damping down inflammatory final pathways by blocking lymph channels. Thus, in analogy to cortisone, hyaluronic acid does not treat the diseases' origin, but rather their symptomalogy.

With respect to the enablement rejection over the method of treatment claims, first and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied

on for enabling support." (Emphasis added.) *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (Emphasis added.) (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 209 USPQ 48 (1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.*

The Examiner has not established any basis to doubt objective enablement, but instead made broad allegations without adequate support. The Examiner has also provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The enablement rejections by the Examiner are thus unfounded. The rejection therefore was improper under *In re Marzocchi.*

The claims rejected are directed to the treatment of inflammatory diseases, the treatment of which are not objectively doubtable, especially in view of various other drugs known in the art, e.g., cortisone, many of which have been even approved by the FDA for multiple indications within the broader class of inflammatory diseases, e.g., ibuprofen. There is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (Fed. Cir. 2005).

As discussed above, this is adequate to objectively enable an invention. Without proper reason or evidence to doubt the objective truth of the enabling disclosure, the Examiner improperly required evidence to prove utility and/or to support enablement. "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *See In re Bundy*, supra.

The rejection starts with the premise, allegation, that the "pharmaceutical art is unpredictable," citing *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) in support. However, there is no basis for such an allegation or conclusion. Fisher does not stand for the proposition that the pharmaceutical art is unpredictable *per se*. The court in *Fisher* stated that "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." Thus, merely concluding that the pharmaceutical art

is unpredictable without looking at the factors involved is an improper basis for the allegation. As discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), used by the Examiner as the basis of the rejections, the court therein teaches that "whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Emphasis added.) No factual basis is provided by the Office Action for the conclusion that the relevant art is unpredictable, which it is not, especially in view of the various drugs known and used in this field.

Additionally, with respect to *Fisher*, the court held therein that the appellant, who was the first to achieve a potency of greater than 1.0 for adrenocorticotrophic hormones ("ACTHs"), had not enabled the preparation of ACTHs having potencies much greater than 2.3, and the claim recitations of potency of "at least 1" rendered the claims insufficiently supported under the first paragraph of 35 U.S.C. §112. Thus, the situation and question considered by the court in *Fisher* is very different than the one present case. The applicant therein was the "first" to achieve a potency of greater than 1.0, but not greater than 2.3, while the claims were directed with an open end to a potency of "at least 1." In the present case, other compounds are already known to treat conditions claimed, and the claims are not open ended.

The law requires merely that applicant disclose the activity of the compounds coupled with knowledge as to the use of said activity, which has been clearly met in the present case. See, for example, *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Additionally, the Office Action alleges that in the pharmaceutical arts, due to its unpredictability each embodiment is required to be individually assessed for physiological activity. However, this is not undue experimentation in the field of pharmaceuticals, but rather an industry wide acceptable routine amount of testing. As discussed in *Wands*, the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

proceed." Here, even the more than three decades old reference cited by the Office Action establishes that at least six models for inflammation were known back than.

While the amount of work may require considerable effort to test various compound of the claims (although not admitted), no undue experimentation is required in determining activity levels. In the pharmaceutical art testing hundreds and thousands of compounds, i.e., screening for activity, is merely routine.

Applicants provide specific guidance as to how the claimed compounds can be tested by providing three *in vivo* examples, each on a different type of inflammation. Yet the Office Action has not found this adequate, and instead alleges that "lack of working example is a critical factor to be considered, especially in a case involving an unpredictable and undevelopled art. See MPEP § 2164."

There are multiple reasons for which applicants respectfully disagree with the above allegation.

First, the MPEP does not provide basis for the above allegation. See MPEP § 2164 is silent on the above issue. See MPEP § 2164.02 teaches that "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." Emphasis added. This factor is nowhere described to be a "critical factor" in the MPEP.

Second, this allegation ignores all the rest of the relevant MPEP section, which states that:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.
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> An applicant need not have actually reduced the invention to practice prior to filing. In Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).
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> The specification need not contain an example if the

> invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).
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> Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. But because only an enabling disclosure is required, applicant need not describe all actual embodiments. (Emphasis added.)

Moreover, there is no "lack of working example." Examples 1, 2 and 3 are working examples.

Additionally, this is not "a case involving an unpredictable and undevelopled art." This art is well developed as clearly supported even by the citation provided by the Office Action to Leshchinskii et al. from 1972.

The Office Action at the end of page 10 and top of page 11 makes various allegations regarding the unpredictability of the invention related to the "structure, formula, or chemical name, of the claimed subject matter" and requires "clear and convincing evidence in sufficient support of making the claimed composition." Applicants assume these allegations are present in the Office Action by error. The drug used in the claimed methods is "hyaluronic acid in crosslinked form" which is clearly identified by name, and which drug is known as evidenced even from the prior art rejections. See also the methods of preparation disclosed on page 3 of the application and at the bottom of page 3 the teaching of commercial sources and trademark names for this drug.

With the current state of the art at the time of filing there is no basis for a rejection for lack of enablement for the claimed indications. At this point it takes merely routine testing/screening, which is not undue experimentation, to determine the activity level of the drug recited in the claims in a variety of known models. Applicants provided adequate support and evidence to enable the method claims. As such, reconsideration is respectfully requested.

Claim Rejections Under 35 USC § 103

The claims are rejected as allegedly unpatentable over Flak in view of Sakurai.

Applicants respectfully disagree with the allegations, but nevertheless amended the claims to achieve an expeditious allowance. The claims now recite that the administration is achieved "intradermally."

Neither Falk or Sakurai teach or suggest the intradermal administration of hyaluronic acid in crosslinked form to the skin. See, e.g., Falk teaching a topically applied composition (see abstract), and Sakurai teaching administration into the eye, etc. (see columns 3 and 4), and use in skin cosmetics (see column 4).

Moreover, Falk teaches hyaluronic acid to be exclusively employed for facilitating penetration of the prostaglandine synthesis inhibitor through the skin and tissue at the site requiring treatment (see, e.g., the abstract). Consequently, hyaluronic acid in the composition according to Falk is not to be regarded as an active ingredient in the sense of the present application, and thus, rather leads away from the present invention.

Additionally, although not necessary for patentability over the cited art, it is believed that the pharmacological effect provided by intradermal administration cannot be achieved by topically applying hyaluronic acid in crosslinked form since exogenous, high molecular weight hyaluronic acid is unable to penetrate the stratum corneum, i.e., the outermost layer of the intact epidermis.

Claims 5 and 6 are rejected as allegedly unpatentable over Flak in view of Sakurai, and in further view of Wilkinson.

Wilkinson does not cure the deficiencies of the primary references. Thus, for at least the reason discussed above, these claims are also patentable.

Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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